EXHIBIT 3

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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MDL No. 1358 (SAS)

In Re: Methyl Tertiary Butyl Ether ("MTBE")
Products Liability Litigation

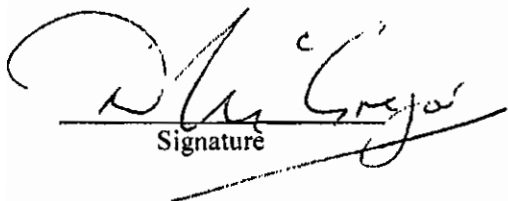Master File
C.A. No. 1:00-1898 (SAS)

This document relates to:

*City of New York v. Amerada Hess Corp., et al.,
Hess Corp., et al.*

No: 04 CV 3417

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EXPERT REPORT OF DOUGLAS McGREGOR, Ph.D

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March 9, 2009
Date

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Opinions on the Toxicology of Methyl *tertiary*-Butyl Ether (MTBE)

9 March 2009

* page numbering can only be approximate, because of the page size difference Europe-USA.

Introduction

I have been asked by Lyondell Chemical Company and Equistar Chemicals LP to review and comment upon the report from Dr. Burns that has been presented by the plaintiffs in the lawsuit filed by the City of New York versus Amerada Hess Corp. et al., 04 Civ 3417. In addition or conjunction therewith, I have been asked for my own opinions with respect to the toxicological profile of MTBE. My comments and opinions, along with the foundation and basis thereof, are set forth below and in my review of MTBE toxicology as published in 2006 in a peer-reviewed journal, a copy of which is attached as Exhibit A to this report and incorporated herein.

Qualifications

My education, experience and training are set forth in detail in the curriculum vitae attached as Exhibit B to this report. In brief, my qualifications to offer opinions on the toxicology pertaining to MTBE include:

- About 25 years of laboratory work, 20 of which were in toxicology using a wide variety of *in vivo* and *in vitro* techniques, either directly or as a study supervisor (SD, PI); this included mutagenicity testing of TBA (published in 1988, my first contact with MTBE) and was followed by

- 11 years employment in carcinogen hazard and risk evaluation in the International Agency for Research on Cancer (IARC), an agency of the World Health Organisation (WHO); this included participation in the *IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans* meeting (1998) at which MTBE was evaluated; followed by

- 9 years occupation as an independent consultant in toxicology with continued involvement in hazard and risk evaluation for non-commercial, national and international organisations –

  - International Programme on Chemical Safety, IPCS;

  - European Food Safety Authority, EFSA;

  - l'Institut National de Recherche et de Sécurité (INRS), France;

  - l'Institut de Recherche Robert-Sauvé en Santé et en Sécurité du Travail (IRSST), Québec, Canada;

  - Republic of Ireland at the Committee for Veterinary Products (CVMP) of the European Medicines Authority (EMEA); and in addition,

  - I have also consulted in toxicology to several commercial enterprises in the petrochemical, metallurgic, pesticide, food and medicinal product areas.

- Several peer-reviewed publications on modes of action of chemical carcinogens;

- Peer-reviewed publications on the toxicology of MTBE and ETBE.

Compensation

My compensation is US$250.00/hr for preparation time; US$125.00/hr for travel time; and US$350.00/hr for court time.

Prior Testimony

I was deposed and I provided trial testimony in the case of South *Tahoe Public Utility District versus Arco et al.* in 2001 and 2002.

I provided testimony in the hearing *Aldéric Morissette and Ville de Québec* in 2008.

I was deposed in the following cases, but did not provide trial testimony: (1) San Jose IBM Workers Litigation in 2003. (2) *D.J.Nelson versus Atlantic Richfield et al.* in 2006 (3) *Suffolk County Water Authority and United Water New York, Inc. versus Amerada Hess et al,* in 2008.

Opinions

The opinions to which I expect to testify to a reasonable degree of scientific certainty are as follows:

1. The existence of "key symptoms" initially reported as associated with MTBE exposure has not been verified;

2. Adverse responses in people exposed to MTBE are highly unlikely to occur at likely or exaggerated exposure levels;

3. Absorbed MTBE is rapidly metabolised primarily to *tertiary*-butyl alcohol (TBA) and formaldehyde and eliminated by volunteers and rodents; formaldehyde (which is also a product of normal metabolism) is very rapidly removed by further metabolism; the kinetics of MTBE strongly suggest that toxicity data obtained following inhalation can be extrapolated to oral exposure;

4. Very high dose levels are required to produce neurological effects in rodents; these effects are reversible within a short time and are not associated with histopathogical lesions;

5. The weight of evidence from rodent and rabbit studies for toxicity to reproduction (fertility or development) is clearly in favour of MTBE not being a human reproductive toxicant at likely or exaggerated doses;

6. The weight of evidence is clearly in favour of both MTBE and TBA, the more long-lived of its primary metabolites, being non-mutagenic;

7. Because of (6) any carcinogenesis of MTBE would involve a non-mutagenic mode of action;

8. While there are reports of increased incidences of various types of tumours in rodent studies with MTBE, TBA and methanol (included as a model, endogenous precursor of formaldehyde without the simultaneous presence of TBA), these are uncertain, inconsistent or, where there is some degree of replication, without human relevance. The weight of evidence is clearly in favour of MTBE not being a human carcinogen at likely or exaggerated doses.

9. Suggestions that have been made for MTBE being damaging in other respects are based on poor evidence.

10. To summarise, in my opinion, MTBE in drinking water has never caused anyone harm and the sufficient and extensive toxicology database strongly suggests it never will cause anyone harm because it shows that MTBE has low toxicity and, should water supplies become badly contaminated, taste and odour will cause self-limitation of intake.

I arrived at the above stated conclusions on the basis of the following general principles and MTBE-specific information to be described later in this document.

General Principles

1. There are identifiable features that distinguish scientific inquiry from other methods of developing knowledge. Scientific researchers propose specific hypotheses and design experiments that test these predictions, but experiments do not necessarily give the same or even similar results when repeated. Consequently, it is a part of scientific method that these experiments are repeated – and the results confirmed - in order to make increasingly dependable predictions of future results. In toxicology, results should be both reproducible and dose-dependent. If these criteria are not met then the hypothesis should be rejected and revised. This ideal situation may not always be met, however, and an evaluation has to be made on the basis of a single experiment. Whenever this is done, any conclusion reached is weaker than when there has been an opportunity to repeat an experiment and collect corroborating information.

2. Commonly used terms that are used in toxicology must be defined, because they may be used differently by other witnesses in this case.

a. "Dose" (OECD, 2003): Total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population. A related term is "Exposure," which is the concentration (c) or amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration (t), i.e., exposure = c x t. "Concentration" can be a quantity of an agent per unit mass or quantity per unit volume.

b. "Hazard" (OECD, 2003): Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system, or (sub)population is exposed to that agent.

c. "Risk" (OECD, 2003): The probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.

3. All substances can be identified as hazards at some dose level. This is a principle that has been fundamental to toxicology for centuries. Hazard is a term that can be applied to any agent if it is present in high enough doses, whereas risk is applied to particular dose or exposure scenarios and may be described as negiligible, moderate, high, severe, etc.

4. Experiments can be used to identify a No Observed Adverse Effect Level (NOAEL), or some other value considered by regulators as being of negligible toxicity within the experiment. The Benchmark Dose (BMD) procedure, which is being used increasingly, provides such an alternative "reference point" (RP) or "point of departure" (PoD). The BMD is based on a mathematical model being fitted to the experimental data within the observable range and estimates the dose that causes a low but measurable response (the Benchmark Response, BMR), typically chosen at a 5 or 10% incidence above the control (U.S. EPA 1995). Such incidence levels would normally be at the limit of statistical significance in toxicological experiments conducted according to internationally agreed guidelines, which take account of both statistical power and animal welfare issues. The BMD lower limit (BMDL) refers to the corresponding lower limits of a one-sided 95% confidence interval on the BMD. Using the lower bound takes into account the uncertainty inherent in a given experiment, and assures (with 95% confidence) that the chosen BMR is not exceeded. It is this more stringent value that provides the RP or PoD, which may be used as an

alternative to the NOAEL. Underlying the use of such terms is the principle that, although there may be negligible effects at this dose level in the experiment performed, should the experiment be repeated, even in the same species, the numerical value obtained may be different, so it cannot be regarded as synonymous with a safe dose.

5. Having obtained an NOAEL, RP or PoD, uncertainty factors (Renwick, 1993; WHO, 1994; Renwick and Lazarus, 1998) are applied that allow for:

a. uncertainty in the initial NOAEL, RP or PoD determination. This is a standard 10-fold that contains factors for differences in toxicokinetics (metabolism, etc.) and toxicodynamics (tissue response in terms of damage).

b. uncertainty in extrapolating from one species (e.g., rat or mouse) to another (e.g., man). This also is a standard 10-fold.

   Thus, species differences and human variability in the basic process of toxicokinetics and toxicodynamics are inherent in the use of data from studies in animals for human risk assessment. An overall factor of 100-fold is usually used to allow for these uncertainties (a and b, above) in the risk assessment of non-genotoxic substances that may or may not also be carcinogenic. Similar uncertainties would be applicable to substances that are both genotoxic and carcinogenic. In addition, however, there are other uncertainties that should be applied specifically for substances that are both genotoxic and carcinogenic and where genotoxicity is a likely mode of action (MOA), because of the inter-individual human variability in cell cycle control and DNA repair, which influence the carcinogenic process (Dorne and Renwick, 2005; EFSA, 2005).

   Before introducing factors for such additional uncertainties, a genotoxic MOA should have been proposed and supported by evidence indicating that this MOA is at least reasonable.

   Uncertainty factors may also be applicable if an LOAEL is used, rather than an NOAEL, if the NOAEL is from a short-term study, rather than a chronic study and if the database is considered to be incomplete in some way. It is to be understood, however, that the application of uncertainty factors is not some mechanical process, but done after careful consideration of the data.

c. The risk assessors, having completed their task, present the data and their conclusions to the risk managers, who may modify the uncertainty factors in a way they see as prudent. The "precautionary principle" is a risk manager's tool and should not also be used by the risk assessors. If the risk assessor was to apply this principle then it will likely be applied twice, so that precaution becomes overly protective and without a sound basis.

Application of these General Principles to MTBE.

1. In the case of MTBE, an overall factor of 100-fold on the NOAEL, RP or PoD would be a reasonable health-based risk assessment conclusion if the basis was carcinogenicity because the database covers all of the endpoints that are normally requested and the tumours that have been reported at increased incidence are:

- of no human relevance although reproducible (Leydig cell adenomas of the rat testis);

- of no human relevance (renal tubule cell tumours specific to male rats); or,

- of uncertain biological status as will be discussed below ("lymphohaematological neoplasms" in female rats in the absence of any report of toxicity in the relevant tissues, hepatic adenomas in female mice at the single very high concentration of 8000 ppm in air, but not at 3000 ppm or lower, and thyroid follicular cell tumours in female mice exposed to TBA, the primary, more persistent metabolite of MTBE).

Although some significant responses have been reported in some studies of genetic toxicity, the overwhelming majority of studies – including all studies *in vivo* – did not show any significant effects in response to MTBE or TBA exposure. Consequently, the genetic toxicity and mutagenicity database does not provide a basis for proposing a genotoxic or mutagenic MOA for any of these reports of higher incidence of tumours. Furthermore, MTBE has never been classified as a genotoxin or a mutagen by national regulators. The increased incidences of these tumours do not, therefore, encourage the application by the risk assessor of safety factors in addition to the 100-fold that would be applied to any endpoint not involving mutagenicity. However, it is not carcinogenicity that provides the Reference Point, Point of Departure or overall NOAEL; this is provided by clinical signs of toxicity in adult rats exposed to MTBE in a two-year inhalation study for chronic toxicity and carcinogenicity in rats (Chun et al., 1992). Similar observations of clinical signs of toxicity were recorded in adult rats during a two-generation study of reproduction (Bevan et al., 1997a). The NOAEL in both of these studies is 400 ppm, equivalent to approximately 150 mg/kg body weight/day in the reproduction study and approximately 140 mg/kg body weight/day in the two-year study. This value therefore encompasses the apparent LOAEL of 400 mg/kg body weight/day in the recent, but less reliable study of testicular toxicity (Li et al., 2008), to which an additional uncertainty factor of up to 10-fold should be applied because 400 mg/kg body weight/day is not an NOAEL but an LOAEL. Thus all three studies provide the same allowable daily intake of MTBE that is predicted not to produce harm.

2. Currently, the most recent authoritative comprehensive review of the data on MTBE is that undertaken by the European Union (EU, 2002). Finland was the rapporteur Member State and the document was discussed in committee throughout its evolution by representatives of all the Member States who were members of the EU at that time. Authoritative documents have also been produced by the Centers for Disease Control (CDC, 1996; WHO/IPCS, 1998) and by Canada, but that work was undertaken much earlier and could not take account of more recent studies (Canada, 1992). There have been other authoritative reviews, but these are more specialised (e.g., IARC, 1999; NTP, 2000).

The EU conclusions on the quantitative aspects of chronic effects were as follows.

a. Inhalation NOAEC of 1450 mg/m^3, based upon a rat carcinogenicity study in which the incidence of Leydig cell tumours was significantly increased at 11,000 mg/m^3 (Chun et al., 1992; Bird et al., 1997). The figure 1450 mg/m^3 resulted in a dose to the rats of approximately 310 mg/kg body weight/day over two years.

b. In searching for a suitable dose on which to assess risk following oral administration, the EU could not completely discard the LOAEL of 250 mg/kg from the study conducted by Belpoggi et al. (1995). Although it was decided to use this study for the derivation of a margin of safety due to lack of other oral carcinogenicity data, the reporting and overall conduct of this study was challenged, and they clearly

did not have complete confidence in the results. These doubts have increased in the intervening years, as will be mentioned below.

This conclusion differs from the earlier conclusion of the CDC (CDC, 1998), in which it is stated (p 115), "An MRL was not derived for chronic-duration oral exposure to MTBE because in the only chronic oral study (Belpoggi et al. 1995), increased mortality occurred in female rats at the lowest dose tested (250 mg/kg/day). Furthermore, the dose of 250 mg/kg/day was associated with dysplastic proliferation of lymphoreticular tissues and an increased incidence of lymphoma and leukemia in female rats." While the first reason (reduced survival) is correct for female rats, the situation was reversed for male rats, in which survival in the high dose group was better than in the control group. The second reason (lymphoreticular pathology) is at least questionable because of the now widely-expressed doubts regarding the biological significance of the lymphohaematopoietic neoplasm incidence.

These three different views will now be used to arrive at Maximum Contaminant Level estimates, using the uncertainty considerations described above and common default values for human body weight (70 kg) and daily water consumption (2L). Other default values for biological parameters were as applied by the US EPA (1988).

1. NOAEL of 400 ppm equivalent to approximately 340 mg/kg body weight/day based on clinical signs of toxicity in rats at 3000 ppm equivalent to approximately 2550 mg/kg body weight/day (Chun et al., 1992; Bevan et al., 1997a) and the application of a basic uncertainty factor of 100-fold.

3400 μg/kg body weight/day = 238,000 μg/person/day.

Therefore the concentration of MTBE in drinking water should not exceed 238,000/2 = 119,000 μg/L.

A risk manager may wish to take public opinion into account and apply a 10-fold uncertainty factor for these concerns. This would reduce the maximum concentration of MTBE in drinking water to 11,900 μg/L. It should be pointed out, however, that there is already extra caution (2-fold) built into the risk assessment value I arrived at: Daughtrey et al. (1997) found no signs of CNS effects or clinical signs of toxicity in rats exposed by inhalation to 800 ppm MTBE for 6h.

2. The EU's LOAEL of 250 mg/kg body weight/day, based on reduced body weight gain in female rats and lymphoreticular pathology at this, the lowest dose level, in a lifetime gavage administration study of toxicity in rats (Belpoggi et al., 1995, 1997, 1998) and the application of a basic uncertainty factor of 100-fold and an additional 10-fold because the dose was an LOAEL, not an NOAEL.

250 μg/kg body weight/day = 17,000 μg/person/day.

Therefore the concentration of MTBE in drinking water should not exceed 17,500/2 = 8,750 μg/L.

3. CDC (at least in 1996) was not prepared to use the Belpoggi et al. study because there was no NOAEL.

Although the first two estimates might not carry a human health risk, it is clear that such concentrations of MTBE would not be tolerated for other reasons, particularly: the taste and odour of the chemical. This is a topic outside of my expertise. In Europe the threshold is accepted as 15 μg/L (15 ppb) (EU 2002).

Discussion

The remainder of this document is largely a response to the opinions expressed by Kathleen Burns, PhD regarding the toxicology of MTBE.

Fundamentally, the position taken by Dr. Burns on the toxicology of MTBE is as follows:

"Based on substantial scientific evidence, MTBE in drinking water is likely to pose health hazards[2] to some members of the public. MTBE caused cancer in animal models that are relied upon by the US government to predict cancer in humans. MTBE damages genetic material and caused other serious health problems in multiple species that the US government relies upon to evaluate the potential for birth defects and other types of damage. There is no credible or proven "safe" level of MTBE exposure and there is substantial and evidence that no safe level exists."

A superficial reading of Dr. Burns' opinions would suggest that they are fully supported by the scientific evidence. In my opinion, however, a more informed reading of Dr. Burns' text, based on knowledge of the scientific evidence that is available, does not support the conclusions and opinions expressed. Furthermore, it is remarkable that, throughout Dr. Burns' long opinion statement, there is hardly a mention of a dose level and no attempt to distinguish hazard from risk. Both dose and risk are fundamental to toxicological evaluation and their absence from Dr. Burns' statement undermines any pretence of expert authority.

The statement by Dr Burns (p5) that there is "no credible or proven 'safe' level of MTBE exposure and there is substantial and [*sic*] evidence that no safe level exists," so that only an undetectable level would be safe are presumably based on the conclusions that MTBE is a carcinogen and its mode of carcinogenic action is mutagenicity. Even if it were arguable that MTBE is carcinogenic, which I do not concede, the overwhelming weight and strength of evidence is that MTBE is not mutagenic.

In the following paragraphs I shall rebut the opinions expressed by Dr. Burns on the toxicology of MTBE and in that process I shall, inevitably, state my own. In addition, I shall state my opinion regarding the suitability of the MTBE toxicology data-base for assessing risks, if any, posed by MTBE as a contaminant of drinking water.

I should like to present as an exhibit my review of MTBE toxicology as published in a peer-reviewed journal: McGregor, D. (2006) Methyl *tertiary*-Butyl Ether: Studies for Potential Human Health Hazards. *Crit.Rev.Toxicol.*, **36**, 319-358. This publication contains many of my opinions on the hazard and risk assessment of MTBE, but as it is now three years since it was published and new data have become available, it will be necessary now to take them into account.

To begin, the behaviour of MTBE and its metabolites within the body need to be described. This information does not, by itself, lead to any conclusions regarding the toxicity of the chemicals, but it is necessary for an understanding of MTBE toxicology.

1. Metabolism and Kinetics

The usual way of describing how long a chemical remains in the body is to state how long it takes for the starting concentration of a chemical to be reduced to half of that concentration. This value is called the $T_{\frac{1}{2}}$ and its units may be seconds, minutes

increased in mice exposed to 8000 ppm MTBE (Dodd & Kintigh, 1989). There exists, therefore, a highly plausible explanation for the increase in cleft palate incidence that was observed only in the 8000 ppm dose group. There were no statistically significant differences in the incidences (up or down) of abnormalities or variations in the 1000 ppm dose group of mice. This NOAEL would deliver approximately 600 mg/kg body weight per day to female mice.

The available evidence is strongly in favour of MTBE not being a cause of human developmental problems at likely or exaggerated dose levels. This is unlike the verdict reached for the lead compounds it replaced in gasoline. The evidence is also contrary to the statements made by Dr. Burns.

7. Neurotoxicity

In the two-generation reproduction toxicity study reported by Bevan et al. (1997a), The F0 and F1 generation rats were examined daily during their pre-breeding period for clinical signs of toxicity. Effects of CNS depression were observed at 8000 ppm (hypoactivity, ataxia, blepharospasms – eye twitching – and a lack of startle reflex) and 3000 ppm (hypoactivity, blepharospasms and a lack of startle reflex). No effects of exposure were observed at 400 ppm, the next lower dose from 3000 ppm. 400 ppm, 6h/day would deliver approximately 40 and 60 mg MTBE/kg bw per day to male and female rats, respectively. The observations made included neurological signs and 400 ppm constituted an NOAEL in this study.

One study was specifically designed to investigate those dose levels at which clinical signs of toxicity appear. This type of study employs a "functional observational battery" (FOB) procedure (Daugtrey et al., 1997), in which observations are made that may reveal more detail than would normally be possible in the routine recording of observations on animals in other standard toxicity assays. Signs indicative of CNS depression were reported 1h after exposure to 8000 ppm and to a lesser extent 4000 ppm, but not at 800 ppm MTBE for 6h in this FOB procedure. These signs were no longer observed 6h or later after exposure. Also, daily exposure at the same exposure levels for 13 weeks demonstrated that the effects were neither persistent nor cumulative. Although body and brain weights were decreased at 8000 ppm, these effects were not accompanied by histological changes in either the brain or the peripheral nerves of the rats (Daughtrey et al., 1997). So, in this study, the NOAEL was 800 ppm. This difference in NOAEL when compared with the 400 ppm found in the Bevan et al. (1997a) two-generation study of toxicity to reproduction is most likely due to the particular dose spacing used (0, 400, 3000 and 8000 ppm in Bevan et al., 1997a and 0, 800, 4000 and 8000 ppm in Daughtry et al., 1997). It should be said that in one inhalation study (Greenough et al., 1980) indications of dose-related CNS depression were reported in rats exposed to 250, 500 or 1000 ppm MTBE 6h/day, 5 days/week for 13 weeks. Possible reasons for such observations that appear to represent outliers in the data-base have not emerged and they are not supported by the experiments just described that were specifically designed to investigate effects on the CNS or any other toxicological experiments in which higher doses were used.

8. Developmental Neurotoxicity

On p44 Dr. Burns states, "Scientific consensus and federal policy establishes that children are … also considered more susceptible to other types of harm, including neurotoxic effects." Greater sensitivity of children in comparison with adults to

neurotoxic effects cannot be generalised in the manner used by Dr. Burns. Furthermore, it would be misleading to suggest that there are no studies that could establish an NOAEL for neurological effects. Probably the largest repository of data on developmental neurotoxicity (DNT) is within the US EPA's pesticide program, because there has been a requirement for DNT testing of pesticides by the Agency for some years. Unfortunately, the data that have been accumulating has been slow to emerge. The Joint Food and Agriculture (FAO)/World Health Organisation (WHO) Meeting on Pesticide Residues in food (JMPR) reviewed the data presented to it by the US EPA in 2002. Data on 14 pesticides were presented. The NOAELs, LOAELs, and toxicity endpoints of each study and of four related studies (on developmental toxicity, multigeneration reproductive toxicity and acute and short-term neurotoxicity) that had been performed with each of the 14 chemicals were compared. The comparison showed that, in general, the NOAELs and LOAELs in the DNT studies were not significantly lower than those in the four related studies. In other words, DNT testing of these 14 pesticides did not reveal a special sensitivity of the developing rats used. This comparison was made on a small number of pesticides, but the database was one that allowed comparisons to be made in an objective fashion with other endpoints of toxicity. A much larger database from the US EPA was presented in March 2007 in a poster session at the Annual Meeting of the Society of Toxicology. Unfortunately, that presentation did not help resolve any of the issues of concern here. No matter the outcome of the current US EPA review, the JMPR (2002) review demonstrates that it is not possible to conclude, even as a generalisation, that all chemicals are more toxic to the developing nervous system than to other developing systems or even to developed systems.

A recent review of developmental neurotoxicity of industrial chemicals lists a few that are recognised causes of neuro-developmental disorders and sub-clinical brain dysfunction. These are: lead, methyl mercury, polychlorinated biphenyls (PCBs), arsenic and toluene and all were said to be more damaging during foetal development (Grandjean & Landrigan, 2006). In the case of toluene, the high exposures *in utero* that were associated with structural defects closely resembling the foetal alcohol syndrome resulted from solvent sniffing by the pregnant women (reviewed in IARC, 1999b). The other organic material listed, PCBs, was a contaminant of cooking oils in two incidents, one in Japan, the other in Taiwan. The *in utero* exposure was clearly associated with a number of growth, structural and behavioural abnormalities (e.g., Rogan et al., 1988), but in neither Japan nor Taiwan was there a clear relationship between symptoms or foetopathy and PCB dose (Yu et al., 1991). In their review, Grandjean & Landrigan list another 196 chemicals that are known to be neurotoxic in man. For none of these is there evidence for them causing DNT. Also, neither MTBE nor TBA is listed.

The use of young non-human animal studies in the identification of human risk factors during post-natal development has been assessed (Brent, 2004). He concluded that epidemiology remains the best way for determining human risk, but the difficulties in doing so using these methods were recognised. Consequently, studies on rodents may remain the only alternative for study of potential risks during development. This is a useful summary review because Brent lists a number of agents (i.e., not all of them are chemicals), describes the effects they produce and makes an assessment of the life-stages most affected by them. A simple count of the various assessments shows that out of 100 agents there were 58 having a greater effect on infant/child; 2 on children and teens; 2 on children and adults; 1 on teens and adults;

and 37 on adults. These figures demonstrate that one cannot assume that infants and children are more sensitive than adults. It will be noted that the two-generation study observations described in 7. Neurotoxicity included observations made on the F1 generarion rats. These animals would have been exposed to MTBE and its metabolites (via maternal blood) from the moment of conception. Therefore, it would be incorrect to suggest that there was no study from which an NOAEL for effects on the nervous system could be established following foetal exposure.

9. Immunotoxicity

Indications of effects upon the immune system could have come from experiments on young adult rats and mice that were exposed to very high concentrations of MTBE. Such studies would have included the studies for up to 2 years in rats and for up to 1.5 years in mice. Immunotoxic effects could been manifest as changes in the weights and histology of spleen and thymus, but no such changes were reported (Chun et al., 1992; Burleigh-Flayer et al., 1992; Bird et al., 1997). No more specific investigations (e.g., investigation of specific cell-types, including T and B cells, resident peritoneal cells and various stem cells in bone marrow) have been conducted. Many *in vitro* methods also are now available. However, such investigations are normally conducted only if there is some particular reason to suspect immunotoxicity. If there is no reason for suspicion of immunotoxicity then they are not routinely expected. For this same reason, no studies of immunotoxic responses following foetal exposure have been conducted. There are few human data, but in a chamber study involving volunteers exposed to 0 or 1.39 ppm MTBE for 1h (Prah et al., 1994) there was no evidence of ocular inflammation as measured by polymorphonuclear neutrophilic leucocytes (PMNs) or increased mRNA coding IL-6 or IL-8 in cells removed from the eye.

10. Human Observations and Consideration of Sensitive Groups

Following promulgation of the Clean Air Act Amendments (CAAA) of 1990, a widespread Oxygenated Fuels Program (OFP) was introduced in the USA in 1992-93. At that time, a number of studies were instigated in response to complaints from the public in certain parts of the country, in particular Alaska. These exploratory studies raised concerns about oxygenated fuels and their principal oxygenate, MTBE, although others do not necessarily support them. Thus, Mohr et al. (1994) found no untoward health effects clearly attributable to MTBE among healthy garage workers. It also seemed anomalous that complaints surfaced only at the time of the CAAA, while oxygenated fuels had been in use for at least a decade before hand, and complaints seemed to be coming from a few OFP regions rather than all of them. Furthermore, in Europe, there seem to have been no similar complaints in spite of fuels in certain countries (e.g., Finland) containing high concentrations (15%) of MTBE. Nevertheless, the (mainly) Alaskan complaints became characterised by a key set of 7 symptoms associated with MTBE exposure. These were: headache, eye irritation, burning sensation in the nose and throat, cough, nausea or vomiting, dizziness and disorientation. It was certainly realised by many of the early investigators that their studies had limitations that were difficult to control and may have affected the results (White et al., 1995; Anderson et al., 1995).

It was proposed that a difficulty in showing a response in an objective study was because people are not equally sensitive to the effects of MTBE. An attempt was made to test this hypothesis in a telephone interview study (Fiedler et al., 1994). It was found that the frequency of symptom reports among people with Multiple